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New Synthetic Approaches to TAT
Final Technical Report

by

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<p>This Final Technical Report describes some additional approaches to 1,3,5,7-tetraacetyl-octahydro-1,3,5,7-tetrazocine, "TAT", related to the former Contract # DAJA 45-85-C-0016; R&D 4480-CH-01.</p> <p>The development of alternative and simple TAT syntheses starting from easily accessible educts still belongs to the very basic and substantial requirements in the area of TAT and HMX research, carried out by the Synthesis Section of ARDC, Picatinny Arsenal, Dover, NJ, USA.</p> <p>In executing this project, the following pathways and approaches have been further pursued and checked experimentally:</p> <p>(1) Cyclization experiments of methylene-bisacetamide "MBA" with formaldehyde.</p> <p>(2) Ring synthetic approaches to TAT, via urea.</p> <p>(3) Additional experiments on the tetramerization of phenyl-methyleneimines ("Roumanian Approach").</p>					
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tetrazocane- Co^{2+} complexes; glycolurils; propellane-glycoluril; partial degradation; bispyrazolo-tetrazocanes; bisimidazo-tetrazocane; hydrogenolytic degradation; macro-cyclic ligand with glycoluril and tetrazocane units (Cucurbiturils); internal/ex-ternal stabilization of TAT; structure and reactivity; synthetic requirements

Block 19 continued

- (4) Synthesis of glycolurils and attempts to cleave the central C-C bond.
- (5) Synthesis of additional bispyrazolo- and bisimidazo-tetrazocanes and reductive destruction experiments.

As discussed in the Final Technical Report of the former Contract, the way leading to stable tetrazocanes is rather small and limited to only very few examples, where the labile 8-membered ring system of the tetrazocanes is either stabilized externally by resonance stabilization of electron withdrawing substituents placed on all four Nitrogen atoms (4-N-Ac \rightarrow TAT; 4-N- $\text{NO}_2 \rightarrow$ HMX, etc.), or internally by ring carbonyl groups adjacent to the ring-N-atoms (amide resonance).

1. Cyclization experiments on methylene-bisacetamide (MBA) with variation of the aldehyde employed, p_{H} -value, temperature, and time (addition of Cs^+), did not lead to any reasonable result or detectable amounts of TAT.
2. Several synthetic approaches to TAT starting from carbonyl-bisurea (triuret) and functional 1-C-equivalents were not successful.
3. By substitution of the anilines employed in the "Roumanian Approach", with electron withdrawing and donating groups did not alternate the weak tendency of tetrazocine formation via phenylmethylenimine.
4. Several kinds of in part novel glycolurils, including also an independent synthesis of a propellane-glycoluril have been synthesized and intensively investigated with regard to the removal of the central C-C bond. However, the energy needed for this ring enlargement is far too high compared with the limited stability of the expected 8-membered ring. A novel polycondensation product of urea, glyoxal and formaldehyde (Cucurbituril) is discussed, consisting of glycoluril and tetrazocane units.
5. Some more novel bis-pyrazolo- and bis-imidazo-tetrazocanes have been made, and the synthesis of the parent compound has been optimized, and their partial destruction has been studied. As it has been found in some model experiments, pyrazole-enamino esters, building parts of these tricycles, can only be reduced under forcing conditions (autoclav, high temperature, etc.) to yield mostly decomposition products or unchanged material, and the same observations have been made on the forementioned tricycles, either they are recovered unchanged or total destruction takes place.

This great number of unsuccessful approaches reflects, once more, the high instability of the desired 8-membered [8]ane- N_4 system, and the difficulty to apply proper conditions, what the final products can stand. These results reveal as well the selective status of the few successfully made tetrazocanes, such as TAT, HMX, etc., known nowadays. Nevertheless, some interesting results pertinent to future TAT syntheses have been found.

1. Summary

This Final Technical Report describes some additional approaches to 1,3,5,7-tetraacetyl-octahydro-1,3,5,7-tetrazocine, "TAT", related to the former Contract # DAJA 45-85-C-0016; R & D 4480-CH-01.

The development of alternative and simple TAT syntheses starting from easily accessible educts still belongs to the very basic and substantial requirements in the area of TAT and HMX research, carried out by the Synthesis Section of ARDC, Picatinny Arsenal, Dover, NJ, USA.

In executing this project, the following pathways and approaches have been further pursued and checked experimentally:

- (1) Cyclization experiments of methylene-bisacetamide "MBA" with formaldehyde.
- (2) Ring synthetic approaches to TAT, via urea.
- (3) Additional experiments on the tetramerization of phenyl-methyleneimines ("Roumanian Approach")
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- (5) Synthesis of additional bispyrazolo- and bisimidazo-tetrazocanes and reductive destruction experiments.

As discussed in the Final Technical Report of the former Contract, the way leading to stable tetrazocanes is rather small and limited to only very few examples, where the labile 8-membered ring system of the tetrazocanes is either externally by resonance stabilization of electron withdrawing substituents placed on all four Nitrogen atoms (4-N-Ac \rightarrow TAT; 4-N-NO₂ \rightarrow HMX etc.) or internally by ring carbonyl groups adjacent to the ring-N-atoms (amide resonance).

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Approach" with electron withdrawing and donating groups did not alternate the weak tendency of tetrazocine formation via phenyl-methyleneimines.

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2. List of Key Words

Synthetic approaches, 1,3,5,7-tetrazocanes, octahydro-1,3,5,7-tetrazocines, TAT, methylene-bisacetamide, MBA, carbonyl-bisurea, 4-substituted phenyl-methyleneimines, tetrazocane-Co²⁺-complexes, glycolurils, propellane-glycoluril, partial degradation, bis-pyrazolo-tetrazocanes, bisimidazo-tetrazocane, hydrolytic degradation, macrocyclic ligand with glycoluril and tetrazocane units, internal/external stabilization of TAT, structure and reactivity, synthetic requirements.

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EXPERIMENTAL PART

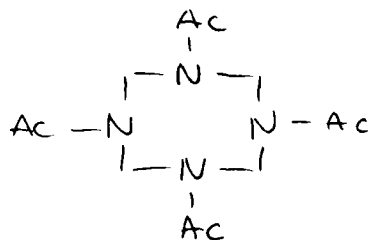
- 9.1 1,3,5-Triacetyl-1,3,5-triazin
- 9.2 Methylenebisacetamide MBA
- 9.3 1,3-Diacetyl-4,5-dihydroxyimidazolidine
- 9.4 4,5-Diacetoxy-1,3-diacetylimidazoline
- 9.5 2,4,6,8-Tetraacetyl-2,4,6,8-tetraazabicyclo[3.3.0]octane
- 9.6 4,5-Dihydroxy-4,5-dimethylimidazoline-2-thione
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- 9.10 Modified Synthesis of 4,5,10,11-Tetrahydrodipyrzolo[1,5-a:1',5'-e][1,3,5,7]tetrazocine-3,9-dicarboxylate, Diethyl
- 9.11 Reactions of Carbonyl-bisurea ("Triuret") with 1-C-functional Reagents
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- 9.13 4,5,10,11-Tetrahydrodipyrzolo[1,5-a:1',5'-e][1,3,5,7]tetrazocine-3,9-dinitrile
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- 9.15 Diethyl 4,5,10,11-tetrahydro-5,11-dimethyldipyrzolo[1,5-a:1',5'-e][1,3,5,7]tetrazocine-3,9-dicarboxylate
- 9.16 7,9,10,12-Tetraazatricyclo[4.3.3]dodeca-8,11-dithione
- 9.17 1,2,4,5-Tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3-one-7-thione
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5. Report (Body of Report)

5.1 Introduction

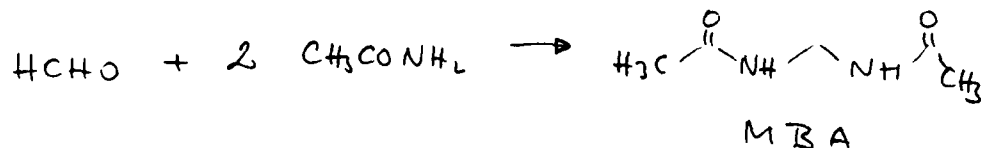
The purpose of this research project was the development of additional synthetic approaches to 1,3,5,7-tetraacetyl-octahydro-1,3,5,7-tetrazocine, its acronym being "TAT"¹⁾



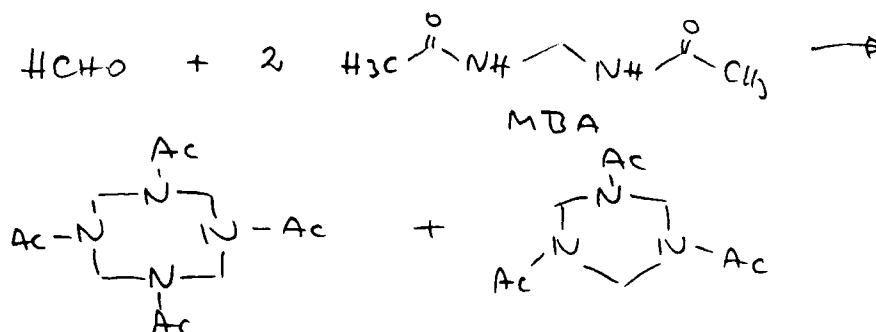
Many of the known synthetic approaches as well as of the physical and chemical properties of TAT and its derivatives are described in the Final Technical Report of the preceding research project named above.²⁾

5.2 Cyclization Experiments of Methylene-bisacetamide (MBA) with Formaldehyde

Methylene-bisacetamide "MBA" is easily accessible from acetamide and formaldehyde³⁾:



In the patent literature is described a synthesis of TAT via MBA⁴⁾. Besides the desired TAT (yield: 18%) also definite quantities of 1,3,5-triacetylhexahydro-s-triazine are formed as side product, from which can be concluded that it might be stemming from a ring contraction reaction of TAT formed primarily:



It seemed to be worthwhile to reinvestigate and to develop further this reaction type under various conditions with the object to optimize the synthetic parameters reported⁴⁾. In this course, a series of experiments has been carried out reacting MBA with formaline, paraformaldehyde and trioxane, respectively. The p_H value was varied stepwise starting from p_H 8 until reaching p_H 12, by adding methanolic KOH. Furthermore, experiments have been carried out treating MBA with formaldehyde with addition of Cesium salts⁵⁾.

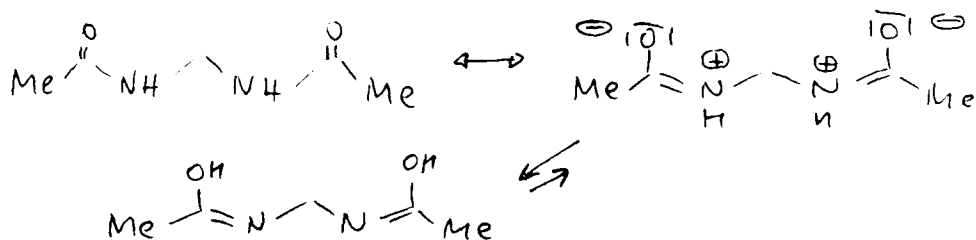
The results obtained are summarized in Table 1.

Monitoring the reaction mixtures with the aid of TLC did not show the formation of any TAT. In most cases, the unchanged starting material could be recovered. At elevated temperatures, the MBA

Table 1. Reactions of MBA with HCHO in the presence of Cs_2CO_3

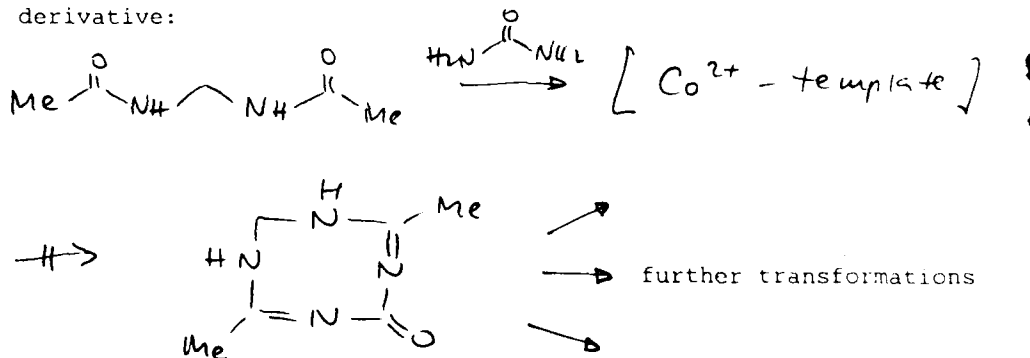
Reagent	Cs salt	Solvent	Reaction conditions	Result
MBA / HCHO (or trioxan, or paraformaldehyde)	Cs_2CO_3	MeCN	RT to 60°C	starting material
MBA / cyclohexa- nedione-1,2	Cs_2CO_3	CH_2Cl_2	60°C	starting material + decomposition products
MBA / cyclohexa- nedione-1,2	Cs_2CO_3	MeCN	80°C / 2d	starting material + decomposition products
N,N'-diisopropylurea/ cyclohexanedione-1,2	Cs_2CO_3	MeOH	RT to 50°C	starting material
N,N'-diisopropyl- urea/cyclohexane- dione-1,2	Cs_2CO_3	EtOH	80°C	starting material + decomposition products
N,N'-diisopropyl- urea/cyclohexane- dione-1,2	Cs_2CO_3	MeCN	80°C / 2d	starting material + decomposition products

was partially destroyed. Under these conditions, even after very extended reaction periods (up to 4 weeks) no TAT was detectable. It seems that under these reaction conditions the MRA is not sufficiently activated to undergo cyclization forming TAT. It cannot be excluded that in MBA the tautomeric forms:



might be predominating in the equilibrium, so that the basicity at the N-atoms is too much diminished for the desired cyclocondensation reactions.

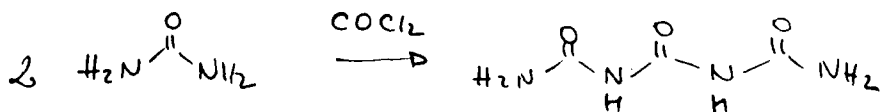
Furthermore, MBA has been reacted with urea under the conditions described by Kadowaki⁶⁾, and in presence of Co^{2+} as potential template metal ion with the hope of obtaining a mono-oxo TAT derivative:

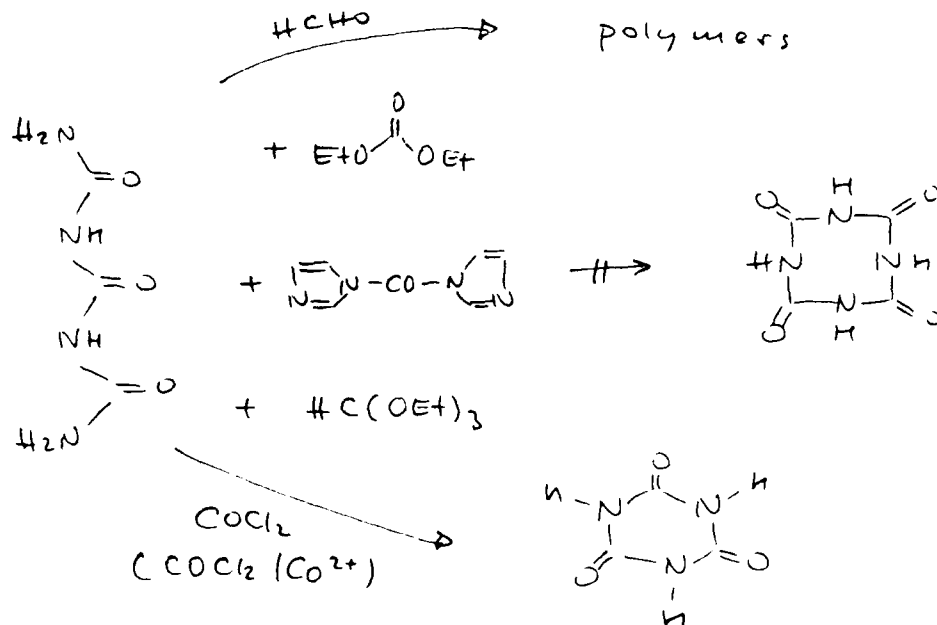


But also this experiment failed.

5.3 Ring Synthetic Approaches to TAT via Urea

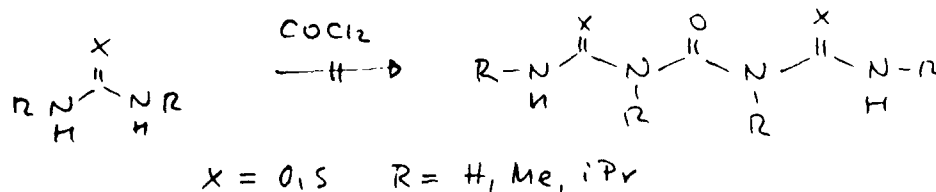
It is known since a long time that urea and phosgene condense in a 2:1 manner to furnish carbonyl-bisurea ("triuret")⁷⁾:





Model considerations reveal that Cs^+ as template ion owns a far too large ion radius for catalyzing a formation of this comparatively small 8-membered [8]ane- N_4 -system.

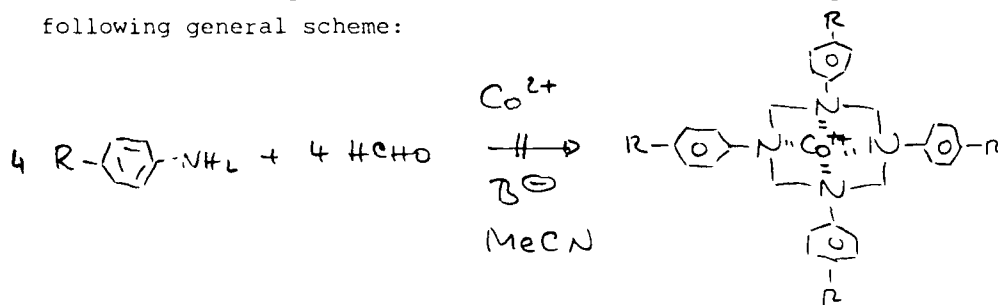
In an independent experiment, it could be proved that also a 2:1-combination of two equivalents urea or thiourea with one equivalent of phosgene is unlikely:



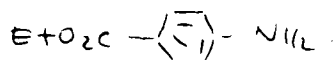
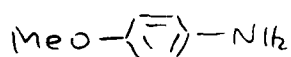
5.4 Additional Experiments on the Tetramerization of Phenylmethyleneimines (Roumanian Approach)

In the Final Technical Report mentioned previously²⁾, an alternative route described by a Roumanian group of Bucurest University⁸⁾ was tried to reproduce. In principle, aniline is treated with formaldehyde in DMF in the presence of $\text{CoCl}_2 \cdot 6 \text{H}_2\text{O}$. After series of unsuccessful experiments, in some cases we were able to isolate a green complex, as described by the authors⁸⁾, which has been analyzed by high-resolution MS to be 1,3,5,7-tetraphenyl-octahydro-1,3,5,7-tetrazocine. However, upon attempts to remove the central Co^{2+} by employing stronger complexing ligands, this complex was rapidly decomposed at the same time.

In the meantime, some more experiments have been undertaken to obtain differently N-substituted tetrazocines according to the following general scheme:



In this course we have employed electron donating as well as electron withdrawing substituents in the 4-position of the anilines employed, e.g.:

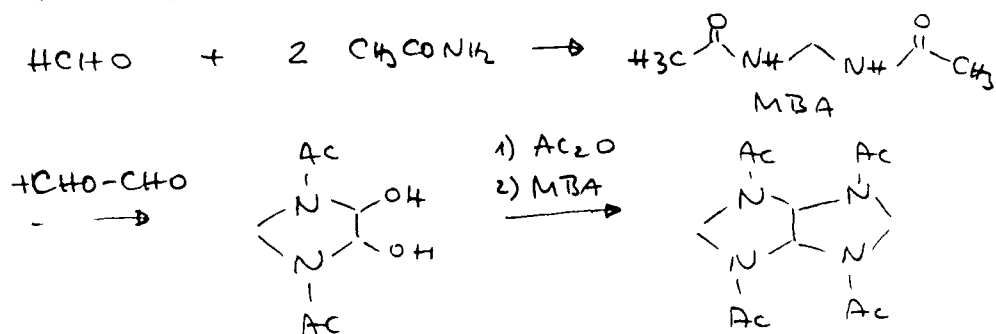


But in all cases investigated no complex formation could be observed. Only in the case of 4-chloroaniline a Co^{2+} -aniline complex has been isolated, but no heterocyclization with the formaldehyde added simultaneously took place.

Thus, this "Roumanian Approach" seems to be strictly limited to aniline itself as shown in our Report²⁾.

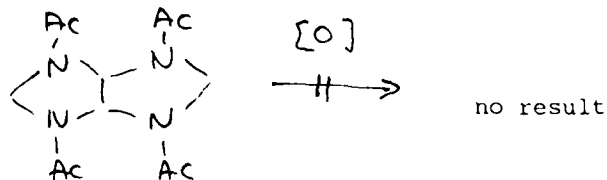
5.5 Synthesis of Glycolurils and Cleaving Attempts of the Central C-C Bond

The only bicyclic molecule that comes nearest to the target molecule TAT, is the N-acetylated 1,3,5,7-tetraazabicyclo[3.3.0]octane or in heterocyclic nomenclature a perhydro-imidazo[4,5-d]imidazole acetylated on all four Nitrogen atoms. This compound is accessible by a 4-step procedure developed recently by Koppes et al⁹⁾:



The starting materials are easily accessible: paraformaldehyde, acetamide, and glyoxal. The final product is a colorless, crystalline compound which differs from TAT only by a central C-C single bond which "divides" the monocyclic TAT into a symmetric perhydro-imidazo[4,5-d]imidazole. Thus, cleavage of this central C-C bond could furnish the desired title compound in a novel and independent way.

Consequently, we have carried out some orientating oxidation experiments:

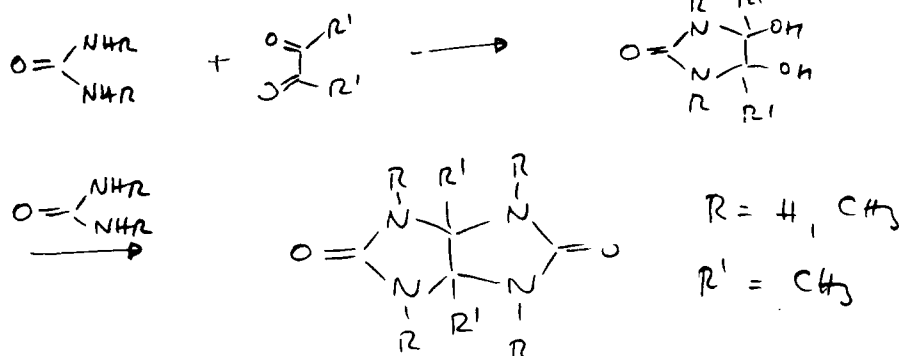


such as, tert-butylhypochlorite, N-bromosuccinimide or refluxing in nitrobenzene, the latter procedure is a well proved method since Skraup's quinoline syntheses and manifold applied for oxidating or dehydrogenating heterocyclic systems^{9a)}.

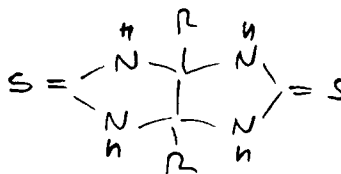
However, in many cases we recovered back our starting material. Sometimes, when refluxing in nitrobenzene a total degradation of the ring system was observed. The energy required for cleaving the central bond seems to be considerably high, so that even the monocyclic TAT formed during this reaction is likewise rapidly decomposed under the reaction conditions applied.

From the model it can be seen that the bicyclic system containing two annulated 5-membered rings is rigid and stable while the resulting 8-membered TAT ring is well known to be rather flexible and therefore much more reactive.

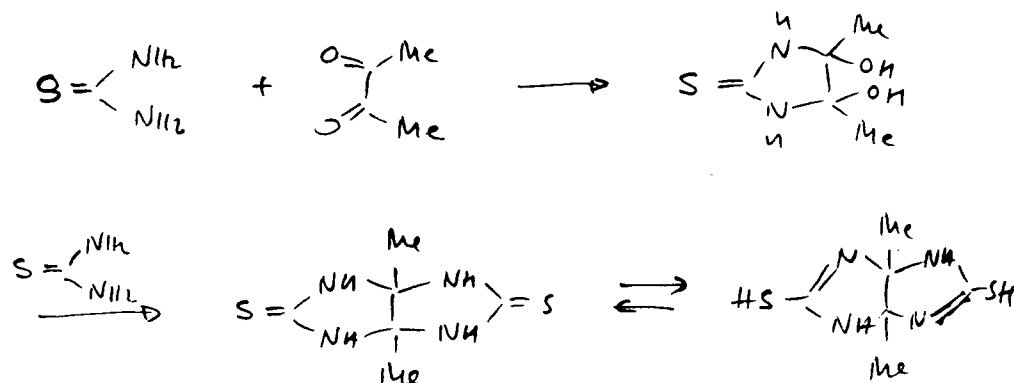
Another promising class of TAT-precursors are the dioxo-derivatives, 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione, also known under the name glycolurils: This class of compounds has been intensively investigated^{2,10)}, and is easily accessible from 1,2-dicarbonyl compounds (glyoxal, diacetyl, benzil) and ureas¹¹⁾:



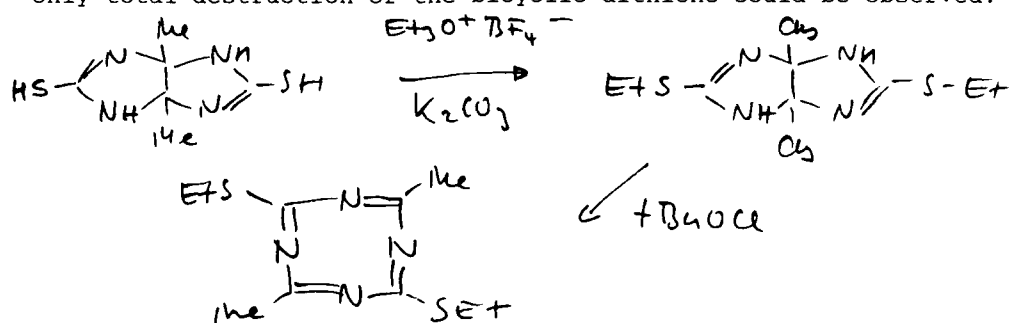
Employing thiourea instead of urea gives the appropriate 3,7-dithio derivatives¹²⁾:



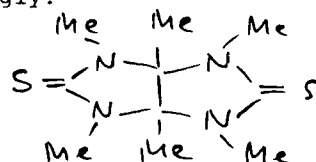
In this course, we have reacted butane-2,3-dione and thiourea leading to the 4,5-dihydroxy-4,5-dimethylimidazoline-2-thione which was successfully cyclized to give the tautomeric dithioxo-glycoluril with a second equivalent thiourea:



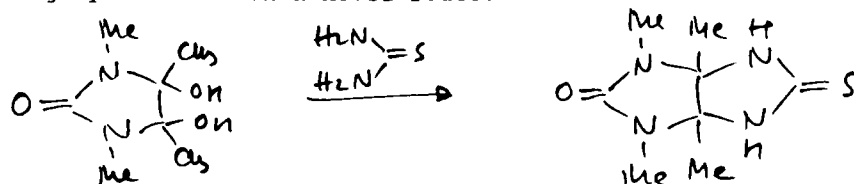
Some experiments have been, furthermore, undertaken to transform these bisureides by a procedure published recently¹³⁾: S-Alkylation, oxidative cleavage of the central bond to the systems reported¹³⁾, only total destruction of the bicyclic dithione could be observed:

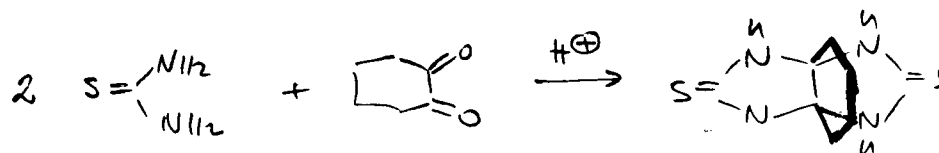


Furthermore, a novel hexamethylated dithioxo-glycoluril has been synthesized accordingly:

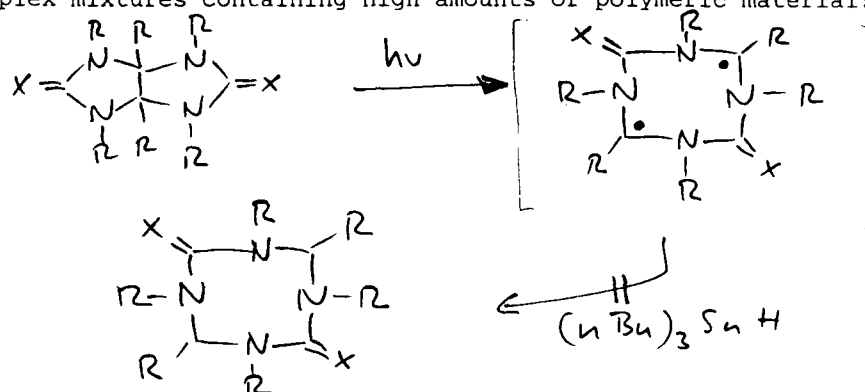


But no further transformation reactions directed to TAT molecules could be achieved. In a recent attempt, also novel mixed oxo-thioxo-glycolurils have been made, as well as 7,9,10,12-tetraazatricyclo-[4.3.3]dodeca-8,11-dithione, glycoluril-propellane, the latter being synthesized on a novel route:





Also photolytic ring enlargement experiments have been carried out. In the presence of $(n\text{-Bu})_3\text{SnH}$, for interception of the expected diradical intermediates, resulted only in rather complex mixtures containing high amounts of polymeric material:



Many polymerization products obtained always in the course of these glycoluril syntheses and transformations can be explained by an observation of Freeman et al¹⁴⁾ that reaction between urea, glyoxal and formaldehyde results in a macrocyclic ligand containing imidazo[4,5-d]imidazole and tetrazocane units, named "Cucurbituril"; the crystal structure has been established¹⁵⁾

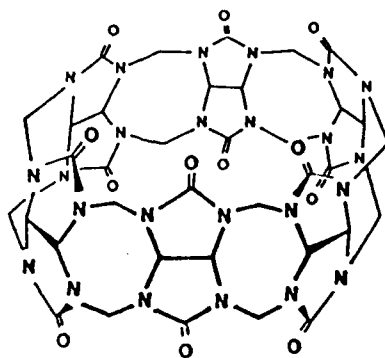
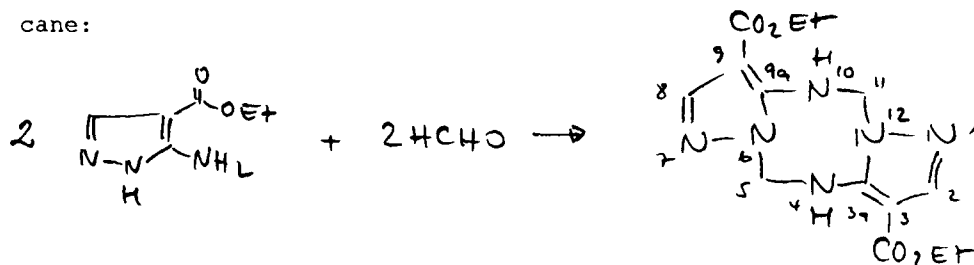


Figure 1. Cucurbituril, a macrocyclic ligand

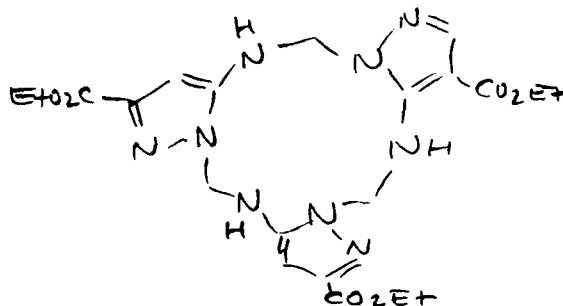
This macrocyclic ligand is nearly insoluble in aqueous solution, and the addition of salts generally results in an enhancement of the ligand solubility, and from this it is concluded that the cations are complexed by the ligand. Thus, a partial destruction of cucurbituril (e.g. complexing a template metal ion) leading eventually to TAT molecules might be a desirable task.

5.6 Synthesis of Additional Bis-pyrazolo- and Bis-imidazo-tetrazocanes and Destruction Experiments

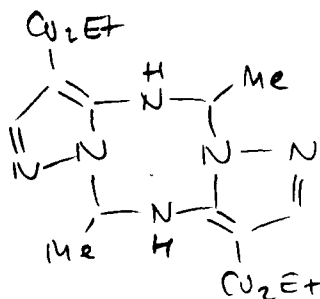
As we have found some years ago, ethyl 5-aminopyrazole-4-carboxylate reacts with formaldehyde to give a bispyrazolo-condensed tetrazocane:



named dipyrazolo[1,5-a:1',5'-e][1,3,5,7]tetrazocine. This synthesis was optimized to give now higher yields (52.5%) of the pure tri-cycle without impurities caused by 3:3-adducts:



In the meantime, this simple and surprising TAT synthesis could be extended also to additional examples of substituted dipyrazolo-[1,5-a:1',5'-e][1,3,5,7]tetrazocines, both the nitrile derivative and the ring-methylated derivative, however, in lower yields:



2 CCOC(=O)N1C=NC(=N1)N + 2 HCHO \longrightarrow CCOC(=O)N1C=NC(=N1)N2C(=C(N2)N3C(=C(N3)N4C(=C(N4)N5C(=C(N5)N6C(=C(N6)N7C(=C(N7)N8C(=C(N8)N9C(=C(N9)N10C(=C(N10)N11C(=C(N11)N12C(=C(N12)N13C(=C(N13)N14C(=C(N14)N15C(=C(N15)N16C(=C(N16)N17C(=C(N17)N18C(=C(N18)N19C(=C(N19)N20C(=C(N20)N21C(=C(N21)N22C(=C(N22)N23C(=C(N23)N24C(=C(N24)N25C(=C(N25)N26C(=C(N26)N27C(=C(N27)N28C(=C(N28)N29C(=C(N29)N30C(=C(N30)N31C(=C(N31)N32C(=C(N32)N33C(=C(N33)N34C(=C(N34)N35C(=C(N35)N36C(=C(N36)N37C(=C(N37)N38C(=C(N38)N39C(=C(N39)N40C(=C(N40)N41C(=C(N41)N42C(=C(N42)N43C(=C(N43)N44C(=C(N44)N45C(=C(N45)N46C(=C(N46)N47C(=C(N47)N48C(=C(N48)N49C(=C(N49)N50C(=C(N50)N51C(=C(N51)N52C(=C(N52)N53C(=C(N53)N54C(=C(N54)N55C(=C(N55)N56C(=C(N56)N57C(=C(N57)N58C(=C(N58)N59C(=C(N59)N60C(=C(N60)N61C(=C(N61)N62C(=C(N62)N63C(=C(N63)N64C(=C(N64)N65C(=C(N65)N66C(=C(N66)N67C(=C(N67)N68C(=C(N68)N69C(=C(N69)N70C(=C(N70)N71C(=C(N71)N72C(=C(N72)N73C(=C(N73)N74C(=C(N74)N75C(=C(N75)N76C(=C(N76)N77C(=C(N77)N78C(=C(N78)N79C(=C(N79)N80C(=C(N80)N81C(=C(N81)N82C(=C(N82)N83C(=C(N83)N84C(=C(N84)N85C(=C(N85)N86C(=C(N86)N87C(=C(N87)N88C(=C(N88)N89C(=C(N89)N90C(=C(N90)N91C(=C(N91)N92C(=C(N92)N93C(=C(N93)N94C(=C(N94)N95C(=C(N95)N96C(=C(N96)N97C(=C(N97)N98C(=C(N98)N99C(=C(N99)N100C(=C(N100)N101C(=C(N101)N102C(=C(N102)N103C(=C(N103)N104C(=C(N104)N105C(=C(N105)N106C(=C(N106)N107C(=C(N107)N108C(=C(N108)N109C(=C(N109)N110C(=C(N110)N111C(=C(N111)N112C(=C(N112)N113C(=C(N113)N114C(=C(N114)N115C(=C(N115)N116C(=C(N116)N117C(=C(N117)N118C(=C(N118)N119C(=C(N119)N120C(=C(N120)N121C(=C(N121)N122C(=C(N122)N123C(=C(N123)N124C(=C(N124)N125C(=C(N125)N126C(=C(N126)N127C(=C(N127)N128C(=C(N128)N129C(=C(N129)N130C(=C(N130)N131C(=C(N131)N132C(=C(N132)N133C(=C(N133)N134C(=C(N134)N135C(=C(N135)N136C(=C(N136)N137C(=C(N137)N138C(=C(N138)N139C(=C(N139)N140C(=C(N140)N141C(=C(N141)N142C(=C(N142)N143C(=C(N143)N144C(=C(N144)N145C(=C(N145)N146C(=C(N146)N147C(=C(N147)N148C(=C(N148)N149C(=C(N149)N150C(=C(N150)N151C(=C(N151)N152C(=C(N152)N153C(=C(N153)N154C(=C(N154)N155C(=C(N155)N156C(=C(N156)N157C(=C(N157)N158C(=C(N158)N159C(=C(N159)N160C(=C(N160)N161C(=C(N161)N162C(=C(N162)N163C(=C(N163)N164C(=C(N164)N165C(=C(N165)N166C(=C(N166)N167C(=C(N167)N168C(=C(N168)N169C(=C(N169)N170C(=C(N170)N171C(=C(N171)N172C(=C(N172)N173C(=C(N173)N174C(=C(N174)N175C(=C(N175)N176C(=C(N176)N177C(=C(N177)N178C(=C(N178)N179C(=C(N179)N180C(=C(N180)N181C(=C(N181)N182C(=C(N182)N183C(=C(N183)N184C(=C(N184)N185C(=C(N185)N186C(=C(N186)N187C(=C(N187)N188C(=C(N188)N189C(=C(N189)N190C(=C(N190)N191C(=C(N191)N192C(=C(N192)N193C(=C(N193)N194C(=C(N194)N195C(=C(N195)N196C(=C(N196)N197C(=C(N197)N198C(=C(N198)N199C(=C(N199)N200C(=C(N200)N201C(=C(N201)N202C(=C(N202)N203C(=C(N203)N204C(=C(N204)N205C(=C(N205)N206C(=C(N206)N207C(=C(N207)N208C(=C(N208)N209C(=C(N209)N210C(=C(N210)N211C(=C(N211)N212C(=C(N212)N213C(=C(N213)N214C(=C(N214)N215C(=C(N215)N216C(=C(N216)N217C(=C(N217)N218C(=C(N218)N219C(=C(N219)N220C(=C(N220)N221C(=C(N221)N222C(=C(N222)N223C(=C(N223)N224C(=C(N224)N225C(=C(N225)N226C(=C(N226)N227C(=C(N227)N228C(=C(N228)N229C(=C(N229)N230C(=C(N230)N231C(=C(N231)N232C(=C(N232)N233C(=C(N233)N234C(=C(N234)N235C(=C(N235)N236C(=C(N236)N237C(=C(N237)N238C(=C(N238)N239C(=C(N239)N240C(=C(N240)N241C(=C(N241)N242C(=C(N242)N243C(=C(N243)N244C(=C(N244)N245C(=C(N245)N246C(=C(N246)N247C(=C(N247)N248C(=C(N248)N249C(=C(N249)N250C(=C(N250)N251C(=C(N251)N252C(=C(N252)N253C(=C(N253)N254C(=C(N254)N255C(=C(N255)N256C(=C(N256)N257C(=C(N257)N258C(=C(N258)N259C(=C(N259)N260C(=C(N260)N261C(=C(N261)N262C(=C(N262)N263C(=C(N263)N264C(=C(N264)N265C(=C(N265)N266C(=C(N266)N267C(=C(N267)N268C(=C(N268)N269C(=C(N269)N270C(=C(N270)N271C(=C(N271)N272C(=C(N272)N273C(=C(N273)N274C(=C(N274)N275C(=C(N275)N276C(=C(N276)N277C(=C(N277)N278C(=C(N278)N279C(=C(N279)N280C(=C(N280)N281C(=C(N281)N282C(=C(N282)N283C(=C(N283)N284C(=C(N284)N285C(=C(N285)N286C(=C(N286)N287C(=C(N287)N288C(=C(N288)N289C(=C(N289)N290C(=C(N290)N291C(=C(N291)N292C(=C(N292)N293C(=C(N293)N294C(=C(N294)N295C(=C(N295)N296C(=C(N296)N297C(=C(N297)N298C(=C(N298)N299C(=C(N299)N300C(=C(N300)N301C(=C(N301)N302C(=C(N302)N303C(=C(N303)N304C(=C(N304)N305C(=C(N305)N306C(=C(N306)N307C(=C(N307)N308C(=C(N308)N309C(=C(N309)N310C(=C(N310)N311C(=C(N311)N312C(=C(N312)N313C(=C(N313)N314C(=C(N314)N315C(=C(N315)N316C(=C(N316)N317C(=C(N317)N318C(=C(N318)N319C(=C(N319)N320C(=C(N320)N321C(=C(N321)N322C(=C(N322)N323C(=C(N323)N324C(=C(N324)N325C(=C(N325)N326C(=C(N326)N327C(=C(N327)N328C(=C

$\text{NaBH}_4/\text{LiBH}_4/\text{TMSCl}$ ¹⁸⁾
 LiAlH_4 ¹⁷⁾
 PtO_2/H_2
 Na -liquid NH_3
 NaBH_4 mixtures in solid state¹⁹⁾.

Accordingly, all reduction experiments carried out on the dipyrazolo-tetrazocines did not give any isolable products. In most cases

the starting material was recovered unchanged, in case of more energetic reduction conditions, almost decomposition was observed and the amount of polymeric materials was significantly increased. Table 2 (cf. page -19-) depicts the reduction methods, conditions, and results obtained.

6. Outlook and Consequences

Almost all forementioned experiments reveal that the development of a novel access to **TAT** and related molecules which can successfully compete with the few useful procedures known today²⁾, is indeed very difficult and limited to a very small ridge trail. Thereby, the weak stability of those 8-membered [8]ane-N₄ systems seems to play the decisive role. All approaches which need more vigorous and energetic reaction conditions do normally not result in the desired 8-membered ring system; but instead, decomposition products and/or polymeric material result from these experiments. On the other side, ring synthetic approaches, even applying template conditions, turn out to be only then successful, when the final [8]ane-N₄ product is internally stabilized, e.g. by the amide resonance. As soon as this internal stabilization elements are tried to alternate chemically, the heterocyclic system shows a total collapse, and decomposition products as well as polymers are the only result.

In this and the precedent research project²⁾, a vast amount of experiments has been investigated, with the aim to approach the **TAT** target molecule from as many sides as possible. But none of all those well-thought proposed routes brought a definite break-through (experts in the TAT field might be not too surprised by these facts).

After all, it is my hope that at least one or two ideas and proposed ways of these Final Technical Reports might serve as a stimulans to develop this field further at a later point, involving appropriate reagents and conditions leading perhaps to a novel entrance to TAT synthesis, perhaps also as simple and elaborate as the main current procedure of partially degradating the urotropine (hexamethylenetetramine) molecule. - To our feeling, at the monent there is no comparative, simple and economic access in sight.

Table 2. Hydrogenation Experiments of the Pyrazole Rings of the Dipyrazolo-
[1,5-a:1',5'-e][1,3,5,7]tetrazocine System

Reagent	Reaction Conditions			Product
	Solvent	Temperature	Time	
NaCNBH ₄	MeOH	80°C	4 h	no reaction
NaCNBH ₄	AcOH	r.t.	5 h	decomposition
NaBH ₄ (10:1) ¹⁹⁾	solid	70°C	8 d	no reaction
	solid	100°C	20 d	no reaction
NaBH ₄	EtOH	80°C	1 d	no reaction
LiAlH ₄	THF/ether	50°C	4 h	polymers
LiAlH ₄	THF	80°C	4 h	polymers
LiAlH ₄ /LiH(1:15)	THF/N ₂	r.t.	4 h	no reaction
		50°C	4 h	decomposition
		80°C	4 h	decomposition
LiAlH ₄ /AlCl ₃ (1:2)	ether	50°C	6 h	decomposition
Na-NH ₃	MeOH	-60°C	1 h	decomposition
10%Pd/C/H ₂	dioxan	100°C	8 h	decomposition
PtO ₂ /H ₂	dioxan	100°C	8 h	no reaction
10%Pd/C/C ₆ H ₁₂	EtOH	60°C	24 H	polymers
LiBH ₄ /Me ₃ SiCl	THF	80°C	4 h	decomposition

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8. Glossary

TAT	1,3,5,7-Tetraacetyl-octahydro-1,3,5,7-tetrazocine
Me ₃ SiCl	Trimethylchlorosilane
HMX	1,3,5,7-Tetranitro-octahydro-1,3,5,7-tetrazocine
TMSCl	Trimethylchlorosilane
NBS	N-Bromosuccinimide
MeOH	Methanol
EtOH	Ethanol
THF	Tetrahydrofuran
t-Bu	tert.-Butyl
MeCN	Acetonitril
MBA	N,N'-Methylenebisacetamide
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
CDCl ₃	Deuteriochloroform
NEt ₃	Triethylamine
BuLi	n-Butyllithium
Me	Methyl
Et	Ethyl
Ph	Phenyl
Ac	Acetyl
AcOH	Acetic Acid
Ac ₂ O	Acetanhydride
AlCl ₃	Aluminium chloride

Δ	Heating Conditions
r.t.	Room Temperature
d	Days
h	Hours
MS	Mass Spectrometry
HR	High Resolution
TLC	Thin Layer Chromatography
IR	Infrared
^1H NMR	Proton Nuclear Magnetic Resonance
^{13}C NMR	Carbon Nuclear Magnetic Resonance
m.p.	Melting Point (not corrected)
4-DMAP	4-Dimethylaminopyridine

9. Appendixes

Experimental Part

9.1 1,3,5-Triacetyl-1,3,5-triazine

In a three-necked flask fitted with dropping funnel, reflux condenser, and inner thermometer 2.4 g of 98% sulfuric acid are added to 20.5 g acetonitrile. The reaction mixture is heated up to 80°C, and to the slightly boiling solution 30 g of trioxan (i.e. 1 mol HCHO) are added in 20.5 ml MeCN. Then 1 h is stirred additionally at this temperature, then the temperature is increased to 145°C, until the reaction mixture does not show any more reflux. After stirring for additional 2 h at this temperature, the color turns to brown; the resulting material is treated with aq. EtOH and recrystallized from the same solvent; yield: 24.8 g (35%) of m.p. 96-98°C. - ^1H -NMR (CDCl_3): δ = 2.08 (s, 10-12-H), 5.12 (s, 2,4,6-H). - ^{13}C NMR (CDCl_3): δ = 21.20 (C-10-12), 56.54 (C-2,4,6), 169.90 (C-7-9).

9.2 Methylenebisacetamide (MBA)

81 g aq. formaline solution (37%, i.e. 1 mole of HCHO) are mixed with 108 g (2 mole) of acetamide in a flask fitted with reflux condenser; then the mixture is gently heated up. At 90°C the mixture is refluxed for 5 h, then the solution is concentrated and the residue is treated with MeOH. The product is recrystallized from acetone; yield: 36 g (27%) of m.p. 190°C

9.3 Diacetyl-4,5-dihydroxyimidazolidine

In a three-necked flask 38.6 g (0.2 mol) of an aqueous glyoxal solution (30%) is brought to a p_H -value of 8.5 with the aid of methanolic KOH solution. Under vigorous stirring 26 g (0.2 mol) of methylenebisacetamide are added and then 10 ml of water for better solution. The resulting suspension is stirred at r.t.. After 5 - 7 d the reaction mixture is filtered and the colorless product is recrystallized from ethanol/acetone; yield: 22 g (59%) of m.p. 171°C.

9.4 4,5-Diacetoxy-1,3-dimethylimidazolidine

18 g (0.1 mol) of the preceding 1,3-diacetyl-4,5-dihydroxyimidazolidine are solved with intense stirring in 250 ml acetic anhydride. Then the mixture is slowly heated to gentle reflux and maintained at that temp. for 2 h. After cooling and removal of the solvent, the oily residue is treated with diethyl ether and left in the refrigerator; recrystallization from diethyl ether; yield: 17.2 g (63%), m.p. 145°C.

9.5 2,4,6,8-Tetraacetyl-2,4,6,8-tetraazabicyclo[3.3.0]octane

A solution of 16.2 g (60 mmol) of the preceding 4,5-diacetoxy-1,3-diacetylimidazolidine and 8.1 g (63 mmol) of N,N'-methylenebisacetamide are solved in 450 ml MeCN and 0.6 g of p-toluenesulfonic acid are added. Upon warming up to 90°C all educts are solved quickly. After 24 h at this temperature, the solvent is evaporated. The oily residue is treated with MeOH and warmed up. The product is precipitated upon cooling; yield 10.3 g (61%), m.p. 240°C. - 1H NMR (CD_2Cl_2): δ = 2.13, 2.35 (2s, 13,14,15,16-H), 4.52, 5.63 (2 d, 9.0, 2-H, 6-H), 6.36 (s, 4-H, 6-H). - ^{13}C NMR (CD_2Cl_2): δ = 22.57 (C-13,14,15,16), 59.8 (C-2,6), 71.9 (C-4,8), 170.2 (C-9,10,11,12).

9.6 4,5-Dihydroxy-4,5-dimethylimidazolidine-2-thione

7.6 g (0.1 mol) of thiourea are solved in 100 ml MeOH and 8.6 g (0.1 mol) of butane dione-(2,3) are slowly added. After stirring for 18 h at r.t. (or 3 h at 60°C), the solvent is evaporated and the resulting oil is treated with $CHCl_3$. Upon cooling, the product is crystallizing; yield: 13.6 g (84%), m.p. 145°C. -

IR(KBr): $\bar{\nu}$ = 3420 (br, OH), 3200 (br, NH), 1110 cm^{-1} (C=S). -
 ^1H NMR (CDCl_3): δ = 1.31 (s, 6,7-H), 3.55 (s, SH), 4.45 (s, NH),
5.80 (s, OH). - ^{13}C NMR (CDCl_3): δ = 19.36 (C-6,7), 92.33 (C-4,5),
183.20 (C-2a), 206.58 (C-2). - MS (m/z) HR for $\text{C}_5\text{H}_{10}\text{N}_2\text{O}_2\text{S}$: calcd.
172.0767; found: 172.0763 (-0.4).
calcd C 37.02 H 10.08 N 28.02
found C 36.89 H 10.02 N 27.88

9.7 1,5-Dimethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dithione

16.2 g (0.1 mol) of the preceding 4,5-dihydroxy-4,5-dimethyl-1,3-imidazolidine-2-thione are solved in 125 ml of MeOH. Then 7.6 g (0.1 mol) of thiourea are added to this solution, then few drops of dil. aq HCl are added and the mixture is stirred for 4 h at 80°C. The colorless precipitate is filtered off, washed with aq. MeOH and dried; yield: 6.25 g (31%), m.p. 195°C (dec.). -
IR(KBr): $\bar{\nu}$ = 3190 (br, NH), 1140 cm^{-1} (C=S). - ^1H NMR (CDCl_3): δ = 1.33 (s, 9,10-H), 7.40 (s, SH), 8.91 (s, NH). - ^{13}C NMR (CDCl_3): δ = 21.02 (C-9,10), 79.25 (C-1,5), 158.91 (C-3a,7a), 179.88 (C-3,7). -
MS (m/z) HR for $\text{C}_6\text{H}_{10}\text{N}_4\text{S}_2$ calcd. 202.0347, found: 202.0329 (-1.8%).
calcd. C 44.19 H 7.42 N 14.72
found C 44.32 H 7.43 N 14.22

9.8 4,5-Dihydroxy-1,3,4,5-tetramethylimidazolidine-2-thione

To a solution of 7.4 g (0.1 mol) of N,N'-dimethylthiourea in 100 ml MeOH are slowly added 8.6 g (0.1 mol) butanedione-(2,3). An exothermic reaction takes place; the reaction mixture is stirred for 2 h at r.t., and then the solvent is evaporated. The crude product is recrystallized from EtOH; yield: 16.7 g (88%), m.p. 142-143°C. - IR(KBr): $\bar{\nu}$ = 3430 (br, OH), 1250 cm^{-1} (C=S). -
 ^1H NMR (CDCl_3): δ = 1.31 (s, 8,9-H), 2.95 (s, 6,7-H), 5.92 (s, OH). -
 ^{13}C NMR (CDCl_3): δ = 19.35 (C-8,9), 28.29 (C-6,7), 91.19 (C-4,5), 181.21 (C-2). - MS (m/z) HR for $\text{C}_7\text{H}_{14}\text{N}_2\text{O}_2\text{S}$ calcd. 190.0803, found 190.0776 (-2.7).
calcd C 44.19 H 7.42 N 14.72
found C 44.32 H 7.43 N 14.22

9.9 1,2,4,5,6,8-Hexamethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dithione

To a solution of 14.8 g (0.2 mol) of N,N'-dimethylthiourea in 250 ml MeOH, 8.6 g (0.1 mol) of butane-dione-(2,3) in 50 ml MeOH are added dropwise. The reaction starts immediately; after addition of few drops of aq. dil. HCl, the mixture is stirred at r.t. for 2 h. Then it is warmed for 2 h to 70°C. After evaporation of the solvent, the precipitate is collected and recrystallized from aq. MeOH.

This product can be obtained likewise from the preceding intermediate and equimolar amounts of thiourea; yield: 18 g (60%), m.p. 184°C (dec.). - IR(KBr): $\bar{\nu}$ = 1280 cm⁻¹ (C=S). - ¹H NMR (CDCl₃): δ = 1.06 (s, 13,14-H), 3.40 (s, 9,10,11,12-H). - ¹³C NMR (CDCl₃): δ = 26.88 (C-13,14), 31.97 (C-9,10,11,12), 117.37 (C-1,5), 182.16 (C-3,7). - MS (m/z) HR calcd. for C₁₀H₁₈N₄S₂: 258.0973; found 258.0995 (+ 2.2).

calcd. C 46.48 H 7.02 N 21.68
found C 46.31 H 6.94 N 20.87

9.10 Modified Synthesis of Diethyl 4,5,10,11-tetrahydrodipyrzolo-[1,5-a:1',5'-e][1,3,5,7]tetrazocine-3,9-dicarboxylate

1.55 g (10 mmol) of ethyl 5-aminopyrazole-4-carboxylate are solved in 500 ml dioxan. Then 1.6 g paraformaldehyde are added as well as a small amount of 4-dimethylaminopyridine (4-DMAP). After refluxing for 24 h, the reaction mixture is cooled to r.t. and the unreacted paraformaldehyde is filtered off. After evaporating the solvent, a colorless oil is obtained which is treated with EtOH to give a solid compound; yield 0.88 g (52.5%), m.p. 194°C. - MS (m/z) = 334.

Side product is a 3:3-adduct; yield 15%; MS (m/z): 501

9.11 Reactions of Carbonyl-bisurea ("Triuret") with functional 1-C-Reagents

Equimolar amounts of carbonyl-bisurea and phosgene give exclusively cyanuric acid and no 8-membered product was obtained.

4 g (25 mmol) of N,N'-carbonyl-bisimidazole ("Staab's Reagent") are mixed with 2.9 g (20 mmol) triuret and heated both in a mortar or a round flask to 100°C. After cooling to ambient temperature, the white solid obtained is washed with water and heated to 140°C in order to remove imidazole by sublimation. However, only pure

triuret is isolated. Also, an addition of 2.5 g $\text{CoCl}_2 \cdot 6 \text{H}_2\text{O}$ does not influence or change this picture.

The same procedure was carried out in 100 ml absol. THF at r.t. for 30 min. No product formation was observed. As well, reaction of triuret (20 mmol) with diethyl carbonate (25 mmol) results only in isolation of the starting material.

After refluxing 2.9 g (20 mmol) of triuret with 2.3 g (16.4 mmol) triethyl orthoformate for 2 h, a white solid is recovered which turns out to be, once again, starting material; as well in this case addition of Co-salts is without influence.

9.12 4-Chloroaniline- CoCl_2 -Complex

2.58 g (10 mmol) of $\text{CoCl}_2 \cdot 6 \text{H}_2\text{O}$ are dissolved in 100 ml DMF and 7.6 g (60 mmol) of 4-chloroaniline in 50 ml DMF are added at r.t., then 4.9 g of a 30% formaline solution (i.e. 60 mmol) in 50 ml of DMF are added under good stirring at r.t.. The solution is colorizing light-blue and a light-blue solid formed during this reaction is filtered off; the reaction mixture is heated to 150°C , and the color turns into green. After 2-6 d maintaining at this temperature, the mixture is allowed to come to r.t. and the excess paraformaldehyde and CoCl_2 are filtered off. After concentration of the solution, the aniline- Co^{2+} complex is isolated as a green crystalline solid; with the aid of MS can be shown that no tetrazocine (even no Co^{2+} -complex) have been formed e.g. as side product. yield: 1.3 g.

9.13 4,5,10,11-Tetrahydrodipyraso[1,5-a:1',5'-e][1,3,5,7]tetrazocine-3,9-dicarbonitrile

1.08 g (10 mmol) of 5-aminopyrazole-4-carbonitrile are solved in 500 ml dioxan. After adding 1.6 g (53 mmol) of paraformaldehyde and small amounts of 4-DMAP the reaction mixture is refluxed for at least 24 h. Then, the unreacted paraformaldehyde is filtered off and the solvent is evaporated. The yellow foamy residue is treated with EtOH, from which it crystallized upon standing at -15°C . The TLC reveals that a product mixture has been formed, which cannot be purified in turn by chromatography due to its instability. However, from MS follows that m/z 240 (2%) according to $\text{C}_{10}\text{H}_8\text{N}_8$ (240.3), one component is the desired tricycle; work to optimize these conditions is under progress.

9.14 Diethyl 4,5,10,11-Tetrahydroimidazo[1,5-a:1',5'-e][1,3,5,7]-tetrazocine-3,9-dicarboxylate

1.55 g (10 mmol) of ethyl 5-aminoimidazole-4-carboxylate is solved in 500 ml dioxan. After addition of 1.6 g (53 mmol) of paraformaldehyde and traces of 4-DMAP it is refluxed for 24 h. After removal of the residual paraformaldehyde and evaporation of the solvent a light-red oil is obtained which is treated with EtOH. After standing at 0°C for several days, a white solid is crystallizing. yield: 180 mg (5.4%); m.p. 215°C. - IR(KBr): $\tilde{\nu}$ = 3430 (NH), 1670, 1530, 1440 cm^{-1} (C=O, C=C).

9.15 Diethyl 4,5,10,11-Tetrahydro-5,11-dimethyldipyrzolo[1,5-a:1',5'-e][1,3,5,7]tetrazocine-3,9-dicarboxylate

1.55 g (10 mmol) of ethyl 5-aminopyrazole-4-carboxylate are solved in 500 ml dioxan, and 1.32 g (30 mmol) of acetaldehyde and traces of 4-DMAP are added. After 24 h of reflux, the solvent is removed in vacuo. The residual white product is recrystallized from EtOH; yield: 840 mg (23%); m.p. 186°C.

9.16 7,9,10,12-Tetraaza-tricyclo[4.3.3]dodeca-8,11-dithione

Independent from a procedure described in the literature (Toray Industries Ltd, Jpn Kokai Tokkyo Koho 57,154,185 (22.11.1982); Chem.Abstr. 98, 160 711j (1983); from 2-aminocyclohexanone oxime with ammonium or alkali thiocyanate, followed by complexation with N-methyl-2-pyrrolidone), a novel simple access to this interesting heteropropellane system has been developed:

3.0 g (40 mmol) of thiourea and 2.2 g (20 mmol) of 1,2-cyclohexanedione are solved in 100 ml MeOH. To this solution, few drops of dil. aq. HCl are added, and the reaction mixture is refluxed for 5 h. On cooling to r.t., a yellow solid is precipitated which is recrystallized from $\text{H}_2\text{O}/\text{MeOH}$ (1:1); yield 3.6 g (84%); m.p. 250°C (dec.). - ^1H NMR ($[\text{D}_6]$ DMSO): δ = 1.35 (2,5-H), 1.66 (3,4-H), 9.04 (NH). - ^{13}C NMR ($[\text{D}_6]$ DMSO): δ = 16.48 (C-3,4), 29.04 (C-2,5), 81.80 (C-1,6), 181.27 (C-8,11).

9.17 1,2,4,5-Tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3-one-7-thione

3.2 g (20 mmol) of the forementioned 4,5-dihydroxy-4,5-dimethyl-

imidazolidine-2-thione are solved in 50 ml of MeOH and 1.76 g (20 mmol) of N,N'-dimethylurea in 30 ml of MeOH are added, as well as few drops of dil. aq. HCl. Then it is stirred for 4 h at 80°C. The white precipitate formed during the reaction is collected after cooling to r.t., washed with aq MeOH and dried; yield 1.46 g (32%), m.p. > 300°C. - IR(KBr): $\bar{\nu}$ = 3280 (br, NH), 1690 (CO), 1140 cm^{-1} (C=S). - ^1H NMR ($[\text{D}_6]$ DMSO): δ = 1.09 (s, 2 C-CH₃), 3.32 (s, 2 N-CH₃), 7.35 (SH), 8.64 (s, NH). - ^{13}C NMR ($[\text{D}_6]$ DMSO): δ = 22.02 (2 C-CH₃), 31.60 (2 N-CH₃), 123.12 (C-1,5), 156.81 (C-SH), 178.23 (C=S), 181.44 (C=O). - MS (m/z) 214 (22%), 155 (100%).

$\text{C}_8\text{H}_{14}\text{N}_4\text{OS}$ (214.2)	calcd.	C 41.58	H 6.93	N 27.73
	found	C 41.22	H 6.51	N 27.31

9.18 Photolysis Experiments

2 g (7.7 mmol) of 1,2,4,5,6,8-hexamethyl-2,4,6,8-tetraazabicyclo-[3.3.0]octane-3,7-dithione (cf. 9.9) is irradiated in 250 ml of acetone (solvent & sensitizer!) for 48 h using a Hg-high-pressure lamp (HPK 125 W) and a Pyrex filter. After working up the reaction mixture, some of the unchanged starting material was recovered as well as an insoluble greenish residue which turned out to be polymeric material. No traces of a 8-membered hexamethyl-tetia-zocine-dithione could be detected.

9.19 Publications from this Contract

There have no publications appeared from our side concerning this research project. This Final Technical Report is the only publication.

9.20 List of Participating Scientific Personnel

(1) Dr. Johannes Nagelschmitz, Dipl.-Chem.

Dr. Nagelschmitz made his PhD-thesis entitled: "Neue Synthesewege zu substituierten 1,3,5,7-Tetrazocanen und 2,4,6,8-Tetraazabicyclo[3.3.0]octanen" in the course of this Research Project. The Mathematisch-Naturwissenschaftliche Fakultät of the Universität Bonn has awarded the PhD-degree on the basis of this thesis.

(2) cand.chem. Marcus Essen

Mr. Essen works as the 2nd Research Scientist within this Project.

He is planning to take parts of his results obtained during these works into his futural Diplomarbeit (MSc-thesis) at the University of Bonn.

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Prof. Dr. Heinrich Wamhoff
Contractor